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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,892	07/11/2006	Jerzy Gebicki	200045-0003-00-US	7625

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EXAMINER	
BLAKELY III, NELSON CLARENCE	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,892	GEBICKI ET AL.	
	Examiner	Art Unit	
	NELSON C. BLAKELY III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-63,65-72,74-84 and 86-89* is/are pending in the application.

4a) Of the above claim(s) *59-62,65-69 and 81-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57,58,63,70-72,74-80 and 86-89* is/are rejected.

7)☒ Claim(s) *57 and 77* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/11/2006, 07/30/2007, 05/12/2008 and 02/27/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 57-64, 70-72, 74-84 and 86-89 are pending. Claims 1-56, 65-69, 73 and 85 are canceled, and claims 59-62, 64 and 81-84 are withdrawn pursuant to Applicant's Amendments (See *infra*). Accordingly, instant claims 57, 58, 63, 70-72, 74-80 and 86-89 are presented for examination on their merits.

Election/Restrictions

Applicant's election ***without traverse*** of Invention I, drawn to a method of treatment or prevention of conditions or diseases associated with dysfunction of vascular endothelium, oxidative stress and/or insufficient production of endothelial PGI_2, in the reply filed on 02/27/2009, is acknowledged.

Claims 59-62, 64 and 81-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made ***without traverse***.

It is acknowledged Applicant elected wherein the disclosed condition or disease is hypertriglyceridemia.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Receipt is acknowledged of the certified copy of the Polish Application No. P-364348, filed 01/12/2004, submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, it is noted that the aforementioned application is not in English.

Information Disclosure Statement

The Information Disclosure Statements, filed 07/11/2006, 07/30/2007, 05/12/2008 and 02/27/2009, are acknowledged and considered to the extent that each reference is a proper citation on a US patent.

The Information Disclosure Statements, filed 07/11/2006 and 07/30/2007, fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because, at least, an English translation of the Abstracts of Foreign Patent Document Nos. DE-840698 and DE840698C, which appear to be similar documents, have not been provided. The documents been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this Information Disclosure Statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Drawings

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, Applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless Applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

Annotated Drawing Sheets

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be submitted or required by the Examiner. The annotated drawing sheet(s) must be clearly labeled as "Annotated Sheet" and must be presented in the amendment or remarks section that explains the change(s) to the drawings.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability.

The drawings are objected to because clean, legible copies of, at least, Figures 1, 9 and 10 are required.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement

sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the Examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Applicant's Amendments

Applicant's Preliminary Amendment, filed 07/11/2006, wherein the specification is amended, claims 1-56 are canceled, and claims 57-85 are added; Applicant's Preliminary Amendment, filed 11/17/2008, wherein claims 65-69, 73 and 85 are canceled, and claim 86 is added; and Applicant's Preliminary Amendment, filed 02/27/2009, wherein claims 87-89 are added, are acknowledged.

Specification

The disclosure is objected to for the following informalities:

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a *single paragraph on a separate sheet* within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The

abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

In Example 2, the term “ant-athrogenic”, in the title, should be replaced with “anti-atherogenic”.

On page 12, line19, the term “weigth” should be spelled correctly as “weight”.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Objections

Claims 57 and 77 are objected to for the following informalities:

With regard to instant claim 57, Applicant is encouraged to use consistent font when referencing formula I in the claim text and structure label, i.e., Times New Roman and Arial, respectively. Additionally, Applicant is encouraged to replace the recitation "NH2, CH3 or N(H)CH2OH", in line 6 of text, with "NH_2, CH_3 or $N(H)CH_2OH$". See instant claims 74-76.

With regard to instant claim 77, Applicant is encouraged to insert the term “a” before the recitation “cardiovascular agent”, in line 2.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57, 58, 63, 70-72, 74-80, 88 and 89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treatment of hypertriglyceridemia, does not reasonably provide enablement for the prevention of said disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in the MPEP § 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

It is noted that all of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The State of the Prior Art and the Predictability or lack thereof in the art

It is noted that the Applicant provides whereas the quaternary pyridinium salt of formula I may be used in the preparation of a vasoprotective agent for the treatment and/or prevention of conditions or diseases, i.e., hypertriglyceridemia, associated with dysfunction of vascular endothelium, oxidative stress, and/or insufficient production of endothelial prostacyclin (PGI_2) on page 1, lines 3-10, of the instant specification. However, the generally accepted definition of "prevent" is to keep from occurring, or to anticipate. Therefore, by the Examiner's broadest reasonable interpretation of the claims to Applicant's method for preventing hypertriglyceridemia, the "prevention" of hypertriglyceridemia lacks enablement due to undue experimentation required to predictably practice the prevention embodiments by Applicant's instant disclosure. Additionally, the art fails to provide compensatory guidance to predictably prevent hypertriglyceridemia. Fung *et al*. (CMAJ, Vol. 167, No. 11, pages 1261-1266; 2002) recite, in the Causes section and Table 1, wherein hypertriglyceridemia may be the result of genetic defects (primary cause), or, more commonly, acquired factors (secondary causes), such as obesity, alcohol consumption and diabetes mellitus. Therefore, because the etiologies of hypertriglyceridemia stem from varying origins, preventing hypertriglyceridemia is unpredictable. Undue experimentation would have been required to practice the invention as broadly claimed. Additionally, the disclosure

is silent with regard to that which makes up and identifies the claimed method for preventing said disease, which is seen to be lacking a clear description via art recognized procedural and methodological steps.

The Amount of Direction or Guidance Present and Presence or Absence of Working Examples

There is no data present in the specification for the "prevention" of said hypertriglyceridemia. The specification only discloses that a quaternary pyridinium salt of formula I may be used in the treatment and/or prevention of conditions or diseases, i.e., hypertriglyceridemia, associated with dysfunction of vascular endothelium, oxidative stress, and/or insufficient production of endothelial prostacyclin (PGI_2) on page 1, lines 3-10, of the instant specification.

The Quantity of Experimentation Needed and the Level of Skill in the Art

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prevent hypertriglyceridemia. The science of drug development has evolved such that, without guidance or working examples in the specification, the claims lack enablement.

Claim 77 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claim recites the limitation, “derivative”, in reference to the instantly claimed compounds and their “derivatives". Applicant has not described the claimed genus of “derivatives” in a manner that would indicate Applicant was in possession of the full scope of this genus, or describe of what this genus is comprised. The instant specification discloses, on page 3, lines 1-4, for example, wherein WO00/40559 discloses therapeutic and cosmetic uses of certain nicotinamide derivatives, 1, 3-disubstituted pyridinium salts, including 1-methylnicotinamide (MNA+) and 1-methyl-N'-(hydroxymethyl)nicotinamide (MNAF+) salts. This exemplification is not a definition that allows the Examiner, or one of ordinary skill in the art, to ascertain that Applicant was in possession of the full scope of this genus.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP § 2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, “not a mere wish or plan for obtaining the claimed chemical invention.” *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office (“PTO”) Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 “Written Description” Requirement (“Guidelines”), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by “showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, “including, *inter alia*, “functional

characteristics when coupled with a known or disclosed correlation between function and structure…" *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although Eli Lily and Enzo were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, Applicants have not described the genus of "derivatives" in a manner that would allow one skilled in the art to immediately envisage the compounds contemplated for use. As such, the claims lack adequate written description for the claimed "derivatives".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 77 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 77 recites the limitation "derivative" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 57, 58, 63, 74-76, 78 and 86-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carlson *et al*. (Atherosclerosis, Vol. 16, pages 359-368; 1972; Cited by Applicant), in view of Gębicki *et al*. (Polish Journal of Pharmacology, Vol. 55,

pages 109-112; 2003; Cited by Applicant), as evidenced by Oettgen *et al*. (Cancer Research, Vol. 20, pages 1597-1601; 1960).

With regard to instant claims 57, 58, 63, 74-76 and 86-89, Carlson *et al*. disclose, in the Summary, a case of massive hypertriglyceridemia with fasting triglycerides, wherein large amounts of chylomicra were present in fasting plasma, and the amounts of low-density (LDL) and high-density lipoproteins (HDL) were very low (See instant claims 87 and 89). In the instant excerpt, Carlson *et al*. further disclose wherein nicotinic acid or nicotinamide was administered to reduce plasma triglyceride levels to about 2-3 mmoles/L and raised the reduced levels of low- and high-density lipoproteins.

Carlson *et al*. fail to disclose specifically wherein formula I comprises a methyl group at the 1-position, or wherein R is CH_3 or $N(H)CH_2OH$; however, Gębicki *et al*. discloses, in the Introduction, the homologue, or analog, 1-methylnicotinamide (MNA+) as one of the two major primary metabolites of nicotinamide (NA). Gębicki *et al*. further discloses, in the instant excerpt, wherein it is well known that NA possesses remarkable anti-inflammatory properties, and that MNA+, similar to NA, is chemically stable, non-toxic and well tolerated. Furthermore, in the Results and Discussion, first paragraph, Gębicki *et al*. discloses that MNA+ can be used to treat a wide variety of skin diseases, for example, and that the use of the compound also provides certain advantages over the use of NA, in particular, an increased efficacy at a specified dose and/or a reduction in undesirable side effects. In the instant excerpt, Gębicki *et al*. further discloses that when used topically, MNA+-containing gel has been shown to produce at least a similar therapeutic effect at concentrations approximately 100 times lower than the

corresponding NA treatment with no appreciable side effects. Additionally, Oettgen *et al*. disclose, in Charts 1 and 2 and Table 1, wherein N-(hydroxymethyl)nicotinamide, wherein instantly claimed R is $N(H)CH_2OH$, and 3-acetylpyridine, wherein instantly claimed R is CH_3, were equally as potent as nicotinamide, wherein instantly claimed R is NH_2, and nicotinic acid (See page 1599, column 2, first full paragraph).

Therefore, a skilled artisan would have envisaged the instantly claimed formula I, wherein R is NH_2, CH_3 or $N(H)CH_2OH$, in the treatment of hypertriglyceridemia, as disclosed by Carlson *et al*., in view of Gębicki *et al*., as evidenced by Oettgen *et al*. One of ordinary skill in the art would have been motivated to combine the teachings of the aforementioned references when seeking a method for treating hypertriglyceridemia, wherein a compound of formula I, with an increased efficacy at a specified dose and/or a reduction in undesirable side effects, is administered. It would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are fairly suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claims 57, 58, 63, 74-76, 78 and 86-89, is *prima facie* obvious over the combination of the aforementioned teachings.

Claims 70-72, 77, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carlson *et al*. (Atherosclerosis, Vol. 16, pages 359-368; 1972), in view of Gębicki *et al*. (Polish Journal of Pharmacology, Vol. 55, pages 109-112; 2003; Cited by Applicant), as evidenced by Oettgen *et al*. (Cancer Research, Vol. 20, pages 1597-1601; 1960), as applied to claims 57, 58, 63, 74-76, 78 and 86-89 above, and

further in view of Bova *et al*. (International Publication No. WO99/06046; Cited by Applicant) and Mathias (U.S. Patent No. 7,153,870B2).

The teachings of Carlson *et al*., Gębicki *et al*. and Oettgen *et al*. have been set forth *supra*.

With regard to instant claims 70-72, 77, 79 and 80, Carlson *et al*. fail to disclose specifically wherein the pyridinium derivative is administered together with a cardiovascular agent; however, Bova *et al*. disclose, in reference claims 33-37, 39 and 40, a method for altering lipids in an individual without causing drug-induced hepatotoxicity, myopathy or rhabdomyolysis, wherein said method comprising administering to the individual once per day a single dose of a pharmaceutical combination comprising an effective lipid-altering amount of nicotinic acid in an extended release form and an effective lipid-altering amount of an HMG-CoA (3-hydroxy-3-methyl-glutaryl coenzyme A) reductase inhibitor, a cardiovascular agent. In the instant excerpt, Bova *et al*. further disclose wherein the lipids may be triglycerides, and wherein the method reduces triglycerides, increases high-density lipoprotein (HDL) cholesterol levels, decreases total cholesterol to HDL-cholesterol levels, and decreases low-density lipoprotein (LDL) cholesterol to HDL-cholesterol ratios in the serum of the subject. In the Abstract, Bova *et al*. disclose wherein the present invention also relates to methods of altering serum lipids in subjects to treat hyperlipidemia, which includes hypertriglyceridemia, by administering an oral solid pharmaceutical combination comprising, at least, an HMG-CoA reductase inhibitor and nicotinic acid, a nicotinic acid compound, i.e., nicotinamide (See reference page 15, second paragraph), or mixtures

thereof. Additionally, Bova *et al*. disclose, on page 21, last paragraph, wherein the reference invention may be formulated into sustained release granules, beads or pellets, tablets, capsules and sachets, for example, as required by instant claims 70, 79 and 80.

Carlson *et al*. fail to disclose specifically wherein the pyridinium salt of formula I is administered parenterally, or to the airways by inhalation; however, Mathias discloses, in column 15, line 5, through column 17, line 50, nicotinamide derivatives formulated for oral administration, i.e., tablets, capsules and liquids; parenteral administration, i.e., intravenous and intraperitoneal; and inhaled/intranasal administration.

Therefore, a skilled artisan would have envisaged the instantly claimed method of treating hypertriglyceridemia, administering a quaternary pyridinium salt of formula I in combination with a cardiovascular agent, i.e., HMG-CoA, as disclosed by Bova *et al*., through customary routes, i.e., oral, parenteral and inhalation, known to one of ordinary skill, as disclosed by Mathias. One of ordinary skill in the art would have been motivated to combine the teachings of the aforementioned references when seeking a combination therapy for the treatment of hypertriglyceridemia, wherein customary routes of administration are available to increase the likelihood of patient compliance. It would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are fairly suggestive of the claimed invention.

Accordingly, the instant invention, as claimed in claims 70-72, 77, 79 and 80, is *prima facie* obvious over the combination of the aforementioned teachings.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 57, 58, 63, 75-79 and 86-89 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-15, 19, 22-25, 37, 53 and 54 of copending Application No. 11/484,892 (hereinafter referred to as '892).

Although the conflicting claims are not identical, they are not patentably distinct from each other because Application No. '892 claims, in reference claims 13-15, 19, 22-25, 37, 53 and 54, a method of treating a lipoprotein abnormality, i.e., hyperlipidemias, which includes hypertriglyceridemia, in a subject in need thereof by administering to the subject a pharmaceutical composition comprising a statin, which is a cardiovascular

agent (See instant claim 77), and a compound of Formula I, wherein R may be NR^2R^3, wherein R^2 is hydrogen and R^3 is either hydrogen or CH_2OH, R^1 is methyl and X^- is a physiologically suitable counter-anion. In the instant excerpt, Application No. '892 further claims a method of raising HDL-cholesterol levels in a subject in need thereof by administering to the subject a pharmaceutical composition comprising a statin and a compound of Formula I.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 57, 58, 63, 70, 75, 78, 80 and 86-89 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 6 and 8 of copending Application No. 11/874,627 (hereinafter referred to as '627).

Although the conflicting claims are not identical, they are not patentably distinct from each other because Application No. '627 claims, in reference claims 1, 5, 6 and 8, a method of treating, orally, a lipoprotein abnormality, i.e., hyperlipidemias, which includes hypertriglyceridemia, in a subject in need thereof by administering to the subject a food extract containing N-methylnicotinamide. It is noted that the instant application claims 1-methylnicotinamide, for example. However, to those skilled in the chemical art, one homologue is not an advance over an adjacent member of a homologous series. The reason for this is that one of ordinary skill, knowing the properties of one member of a series, would reasonably expect the properties in

adjacent members to be substantially similar. *In re Henze*, 85 USPQ 261 (1950). *In re Wood*, 199 USPQ 137 (C.C.P.A. 1978) and *In re Lohr*, 137 USPQ 548, 549 (C.C.P.A. 1963).

Accordingly, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NELSON C. BLAKELY III whose telephone number is (571) 270-3290. The examiner can normally be reached on Mon - Thurs, 7:00 am - 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Phyllis G. Spivack/
Primary Examiner, Art Unit 1614
April 10, 2009

/N. C. B. III/
Examiner, Art Unit 1614